Clinical Features:
Premature Ovarian Failure (POF, also known as primary ovarian insufficiency), is the loss of predictable ovarian follicle function resulting in amenorrhea before the age of 40\(^1\). Patients often have follicle-stimulating hormone (FSH) levels in the postmenopausal range\(^2\). Ovarian function may be intermittent, and spontaneous conceptions have been reported in 5-10% of patients with POF\(^1\). There are several etiologies of premature ovarian failure, including endocrinopathies, autoimmune disease, chromosomal abnormalities, and gene mutations\(^3\). Approximately 10% of cases of POF are familial\(^2\).

**Our Premature Ovarian Failure Sequencing and Deletion/Duplication Panels include analysis of the 10 genes listed below.**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Clinical Features</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMP15</td>
<td>Premature Ovarian Failure, Ovarian Dysgenesis</td>
<td>Nonconservative heterozygous mutations in BMP15 have been identified in patients with POF. The majority of mutations are found in the proregion of the BMP15 pre-protein and appear to reduce the production of mature BMP15 peptide dimers(^4).</td>
</tr>
<tr>
<td>FIGLA</td>
<td>Premature Ovarian Failure</td>
<td>Heterozygous mutations in FIGLA have been described in two patients with POF. Both mutations identified are deletions; one results in premature termination of the protein while the other removed a single amino acid altering binding of FIGLA to TCF3(^5).</td>
</tr>
<tr>
<td>FOXL2</td>
<td>Blepharophimosis, Epicanthus Inversus and Ptosis syndrome (BPES), Premature ovarian failure</td>
<td>BPES is an autosomal dominant disorder characterized by eye abnormalities and facial features, and POF is observed in type I BPES(^6). A wide range of FOXL2 mutations have been observed in patients with BPES type I as well as isolated POF(^6).</td>
</tr>
<tr>
<td>FSHR</td>
<td>Ovarian Dysgenesis, Ovarian Hyperstimulation syndrome</td>
<td>Mutations in the FSHR gene have been found in patients with ovarian dysgenesis with an apparently recessive inheritance pattern(^7,8). Ovarian hyperstimulation syndrome, characterized by hyper-reactive luteinized cells during pregnancy, has also been linked to FSHR mutations(^9).</td>
</tr>
<tr>
<td>HFM1</td>
<td>Premature Ovarian Failure</td>
<td>Compound heterozygous mutations of HFM1 have been identified in several patients with POF, including missense and splice site mutations(^10).</td>
</tr>
<tr>
<td>LMNA</td>
<td>Malouf syndrome</td>
<td>Malouf syndrome is a cardiomyopathy syndrome with symptoms of dilated cardiomyopathy, mitral or tricuspid valve insufficiency, lipodystrophy and premature ovarian failure(^11). Malouf syndrome is inherited in an autosomal dominant manner and is associated with a wide spectrum of mutations in LMNA.</td>
</tr>
<tr>
<td>MCM8</td>
<td>Premature Ovarian Failure</td>
<td>A homozygous missense mutation in MCM8 was identified in three sisters with POF(^12). Functional studies demonstrated decreased function of the mutant protein in chromosome break repair(^12).</td>
</tr>
<tr>
<td>NOBOX</td>
<td>Premature Ovarian Failure</td>
<td>NOBOX-associated POF is an autosomal dominant form of POF that is characterized by reduced or absent follicles, delayed or absent puberty and amenorrhea(^13,14).</td>
</tr>
<tr>
<td>NR5A1</td>
<td>Premature Ovarian Failure, 46,XY Sex Reversal</td>
<td>NR5A1 mutations have been observed in families with 46,XX POF and 46,XY disorder of sexual development in the same family and are associated with both phenotypes(^15).</td>
</tr>
<tr>
<td>PSMC3IP</td>
<td>Ovarian Dysgenesis</td>
<td>A homozygous in-frame deletion in PSMC3IP was found to segregate in a large family with ovarian dysgenesis(^16).</td>
</tr>
</tbody>
</table>
Premature Ovarian Failure Sequencing Panel (10 genes sequencing)

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $2000
CPT codes: 81407
Turn-around time: 8 weeks

Premature Ovarian Failure Deletion/Duplication Panel (10 genes deletion/duplication analysis)

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $1545
CPT codes: 81407
Turn-around time: 6 weeks

Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interest are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All novel and/or potentially pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Results:
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:
3. Premature Ovarian Failure: Clinical Presentation and Treatment.


Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS’ NEEDS